

## ORIGINAL ARTICLE

# Prospective, placebo-controlled trial of 5 vs 10 days of oral prednisolone in acute adult asthma

A. M. JONES\*, M. MUNAVVAR\*, A. VAIL<sup>†</sup>, R. E. ALDRIDGE\*, L. HOPKINSON\*, C. RAYNER\* AND B. R. O'DRISCOLL\*

\*Department of Cardio-Respiratory Medicine, Hope Hospital, Stott Lane, Salford, M6 8HD, U.K. <sup>†</sup>Biostatistics Group, University of Manchester, Hope Hospital, Stott Lane, Salford, M6 8HD, U.K.

**Abstract** *Background:* The optimal duration of oral steroid treatment in the management of acute adult asthma is unclear. We prospectively studied the effect of 5 vs. 10 days of oral prednisolone in patients with acute asthma requiring hospital admission. *Methods:* Each patient received 40 mg of enteric-coated prednisolone daily for 5 days, followed by 5 days of 40 mg prednisolone daily ( $n=24$ ) or placebo ( $n=20$ ). All were given their usual inhaled asthma therapy including inhaled corticosteroids. Patients kept PEF and symptom diaries for 21 days.

*Results:* For the 5-day treatment group mean (95% CI) early morning PEF was 6 (–47, +36) l/min lower to day 21 ( $P=0.78$ ). There was no evidence of differences in other PEF measures (morning post-bronchodilator, evening or worst of day). One patient in each group had an exacerbation requiring further oral steroids during the 21-day observation period. Asthma symptom scores were worse in the 5-day group on days 6–21 but the significance of this finding was uncertain, as a difference had emerged by day 5 (prior to trial entry). *Conclusions:* It may be possible to reduce the standard steroid course to 5 days in acute adult asthma, provided all patients receive inhaled steroids and a personal asthma management plan. © 2002 Elsevier Science Ltd. All rights reserved.

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## INTRODUCTION

Systemic corticosteroids are well established in the management of acute asthma. The optimal dose and duration of therapy is however unknown. Different dose regimes have been studied (1–3). A 10-day course of prednisolone with abrupt termination has been shown to be as effective as a 17-day tapering course (4). British Thoracic Society guidelines suggest 30–60 mg of prednisolone for 7–21 days (5). The potential benefit of corticosteroid therapy must be balanced against the possibility of cumulative steroid side-effects for patients who are likely to receive several such courses during their lifetimes (6). There is increasing concern that a patient's risk of osteoporosis may be related to the cumulative dose of systemic corti-

costeroid therapy (7). However, it is essential that a sufficient course be given to ensure full recovery from the episode of acute asthma. Paediatricians, conscious of the growth stunting effect of systemic steroids, tend to prescribe shorter courses than adult physicians. We have compared a 5-day course of prednisolone with a 10-day course for the treatment of adults admitted to hospital with acute asthma.

## METHODS

The study was performed at a single centre, in an 850-bed teaching hospital in Salford, United Kingdom, following the approval by the local research ethics committee.

Each patient received 40 mg of enteric-coated prednisolone daily for 5 days, followed by a further 5 days of 40 mg prednisolone or placebo tablets daily. All were treated with nebulised bronchodilators for 2–5 days. All were discharged on inhaled beta-agonist and inhaled steroid therapy.

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Correspondence should be addressed to: Dr B.R. O'Driscoll, Department of Cardio-Respiratory Medicine, Hope Hospital, Salford, M6 8HD, U.K. Fax: +44 161 787 4328; E-mail: [Ronan.O'Driscoll@srht.nhs.uk](mailto:Ronan.O'Driscoll@srht.nhs.uk)

Patients were assessed on the medical wards at Hope Hospital during admission for acute asthma exacerbation. All eligible patients were interviewed by one of the investigators and asked if they would be willing to participate in the study. Written consent was obtained in each case. Inclusion criteria were acute adult asthma (peak expiratory flow {PEF} < 65% predicted), admission to hospital under the care of designated adult physicians, age 16–60 years, ability to give informed consent and to maintain a PEF diary for 21 days and use of inhaled steroid on discharge. The predicted PEF for each patient was calculated using published formula for standard laboratory normal values (8). Exclusion criteria were: major medical illness (such as pneumonia, heart failure, lung cancer, and bronchiectasis), chronic pulmonary disease other than asthma, requirement for mechanical ventilation prior to randomisation, use of long-term oral corticosteroids, use of nebulised corticosteroids or any recent use of oral corticosteroids prior to admission. Demographic and medical information was recorded by one of the investigators. Patients were issued with a trial diary and a Mini-Wright peak flow meter (Clement Clark International, London, U.K.) and instructed on its use. Patients were entered in a double-blind fashion. Randomisation codes (5- or 10-day course) were sealed in opaque brown envelopes and shuffled into random order and then numbered sequentially. The investigator selected the next numbered envelope for each patient and sent it unopened to a non-blinded hospital pharmacist with a prescription for “steroid trial tablets”. The non-blinded pharmacist ensured that all patients received the correct tablets. Patients were provided with 40 mg prednisolone daily for the first 5 days, supplied as 5 mg prednisolone enteric-coated tablets. For days 6–10, each patient received 8 tablets per day of enteric-coated prednisolone or an identical placebo tablet (supplied by Pfizer Ltd, Sandwich, U.K.). All patients were also issued with a supply of open-label prednisolone (40 mg for 5 days) for emergency use and instructed that this should be taken in the event of deteriorating asthma and recommended to self refer to hospital under these circumstances.

All other asthma treatment was at the discretion of the patient's personal physician subject to a requirement for all patients to receive inhaled steroid treatment equivalent to at least 400 mcg of beclomethasone dipropionate per day. The physicians were allowed to remove the patient from the study at their own discretion. A letter was sent to the patient's general practitioner explaining the nature and purpose of the trial. All patients were given a 4–6 week follow-up appointment in the outpatient clinic where they were reviewed by one of the investigators and their diary cards were collected.

Patients were asked to record their PEF on waking, 30 min after their first bronchodilator treatment of the

day and at bedtime before inhaled treatment. They were also asked to record their PEF at other times if they felt breathless (worst daily PEF). Patients recorded their asthma symptoms daily on a numerical score with verbal descriptions (modified Likert scale; 1=no symptoms, 2=very mild, 3=mild, 4=moderate, 5=quite bad, 6=very bad, 7=worst possible symptoms). The principal outcome measures were waking PEF and asthma exacerbations. Secondary outcomes were post-bronchodilator morning PEF, evening PEF, worst PEF on each day, symptom scores (overall asthma severity, wheeze severity, cough severity, nocturnal asthma symptoms) and beta-agonist use.

## STATISTICAL ANALYSIS

For each individual, mean PEF and symptom scores following randomised allocation were calculated. These mean scores were compared between groups using analysis of covariance in Stata version 6.0. This allowed adjustment for differences between individuals by controlling for the mean score for each patient prior to day 6 treatment. Occasional missing values from diary cards were assumed to be missing at random.

The study was designed to recruit 75 patients in order to have 60 patients for analysis. This was calculated to give 80% chance (power) of detecting a 15% difference in morning PEF between two groups of patients (calculated from a previous trial of similar design) (4). The trial stopped early due to slow recruitment, the trial was designed to run in two centres but one centre was unable to recruit due to the relocation of the proposed co-investigator.

## RESULTS

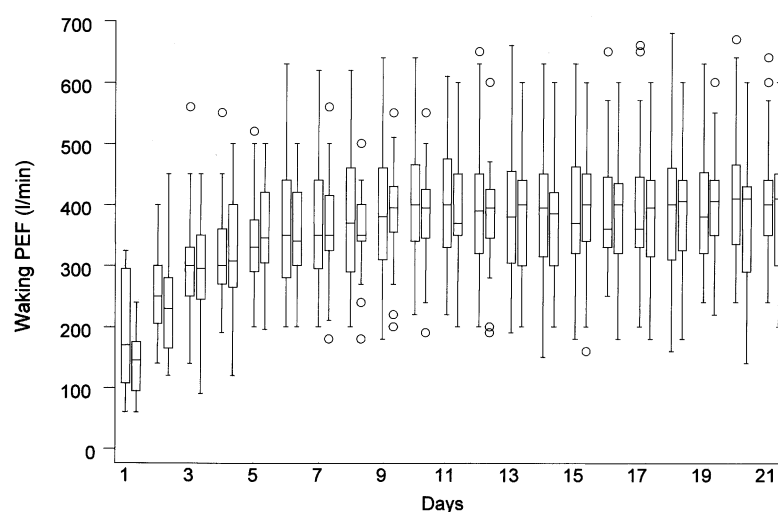
Forty-seven patients entered the study of whom 44 completed the study, 20/22 in the 5-day treatment group and 24/25 in the 10-day treatment group. The two groups of asthmatic patients had similar demographic features, except for a higher proportion of patients taking a long-acting beta agonist in the 10-day treatment group (Table 1). Two patients in the 5-day group and 1 patient in the 10-day group failed to complete diaries; none of these three patients required readmission or rescue oral corticosteroid treatment and all, at follow-up, were judged by their physician to have made a satisfactory recovery from their acute asthma.

The groups were similar during the open-label steroid treatment, with a mean early morning PEF of 296 and 306 l/min for the 5- and 10-day oral steroid treatment groups, respectively. The two groups remained similar during the randomised phase and throughout the observation period to day 21 (Fig. 1). Each of the other

**TABLE 1.** Patient demographics

	10-day oral steroid treatment group (n=25)	5-day oral steroid treatment group (n=22)
Sex:		
Male	7	9
Female	18	13
Age (years)*	29.8 (11.3)*	32.0 (11.0)*
Positive history of atopy	14	12
Smokers:		
Current	7	6
Ex	2	4
Predicted mean PEF (l/min)*	478 (103)*	470 (74)*
Duration of Asthma (years)*	9.6 (11.4)*	10.4 (12.0)*
Oral theophylline	3	2
Long-acting inhaled beta agonist	5	2
Mean dose of inhaled steroid (beclomethasone or equivalent, mg)*	1.060 (0.544)*	0.896 (0.437)*

\*values expressed as mean (SD).



**FIG. 1.** Morning waking PEF. Daily results in pairs: 10-day treatment group first, 5-day treatment group second. Vertical boxes = interquartile range, middle horizontal bar = median value, vertical spikes = expected range (dots demonstrate unusually large or small values outside expected range).

PEF measurements was not significantly different between the groups (Table 2).

Mean symptom scores were similar during the initial 5-day open-label phase (Table 3). However, the mean overall symptom scores on day 5 (when all patients had identical therapy) were 3.2 out of seven in the 5-day group and 2.6 out of seven in the 10-day group. Although symptoms reduced with time in both groups, the overall symptom score ( $P=0.01$ ), wheeze ( $P=0.002$ ) and nighttime symptoms ( $P=0.04$ ) were significantly higher in the 5-day group than in the 10-day group for the remainder of the study (Table 3). There was no evidence of significant differences in the cough scores recorded ( $P=0.18$ ).

There were no deaths in either group. No patients required assisted ventilatory support. One patient in each group had an exacerbation requiring further oral steroids during the 21-day observation period, during days 17–20 (10-day treatment group patient) and days 10–15 (5-day treatment group patient). There was one late exacerbation in the 10-day treatment group who required readmission to hospital (day 25) and a further course of oral steroids. No patients in the 5-day treatment group required readmission, but one other patient did require a further course of oral steroids in the late follow-up period starting at day 36.

**TABLE 2.** Mean (SD) of individuals' mean PEF

Time	10-day group		5-day group		Group difference <sup>a</sup>	
	Open label	To day 21	Open label	To day 21	Mean (95% CI)	P-value
Waking	306 (79)	398 (103)	296 (82)	383 (90)	−6 (−47,36)	0.78
30 min <sup>b</sup>	355 (83)	435 (94)	341 (92)	415 (93)	−4 (−37,30)	0.83
Bedtime	357 (86)	427 (99)	348 (84)	405 (93)	−16 (−50,18)	0.35
Worst	273 (69)	389 (100)	277 (82)	371 (87)	−20 (−63,23)	0.36

<sup>a</sup>Estimated from analysis of covariance: negative difference implies lower (worse) mean value in 5-day group.

<sup>b</sup>PEF measured 30 min after morning dose of inhaled bronchodilator.

**TABLE 3.** Mean (SD) of individuals' mean asthma symptom scores on a scale from 1 (no symptoms) to 7 (worst possible symptoms)

Symptom	10-day group		5-day group		Group difference <sup>a</sup>	
	Days 1–5	Days 6–21	Days 1–5	Days 6–21	Mean (CI)	P-value
Overall severity	3.8 (1.0)	1.9 (0.8)	3.8 (1.3)	2.6 (1.1)	0.6 (0.1,1.1)	0.01
Wheeze	4.0 (1.0)	1.9 (0.9)	3.8 (1.4)	2.6 (1.1)	0.8 (0.3,1.3)	0.002
Cough	4.1 (1.2)	2.1 (1.1)	4.0 (1.5)	2.4 (1.1)	0.4 (−0.2,0.9)	0.18
Nighttime	3.6 (1.4)	1.8 (1.0)	3.7 (1.4)	2.4 (1.1)	0.6 (0.0,1.2)	0.04
Salbutamol puffs	22.2 (11.6)	5.8 (3.7)	20.6 (12.2)	4.8 (3.6)	−0.9 (−3.3,1.5)	0.45
Beclomethasone puffs	3.7 (1.7)	4.5 (1.7)	3.8 (1.8)	4.7 (1.5)	0.0 (−0.6,0.7)	0.93

<sup>a</sup>Estimated from analysis of covariance: positive difference implies higher (worse) mean value in 5-day group.

## DISCUSSION

This study addresses an important clinical question, the length of steroid treatment after an asthma exacerbation. A reduced duration of oral steroid treatment after an exacerbation would be of clinical importance as it would reduce the total steroid load and thus favourably reduce serious steroid side-effects. However, a shortened course must not place patients at risk from their asthma. The study was designed as a randomised, double-blind, placebo-controlled trial to compare the effects of taking a 5-day course of oral prednisolone 40 mg to a 10-day course with the same drug at the same dosage in adults admitted to hospital because of acute asthma. The final results must be interpreted with caution, as the number (44) of patients who completed the study was below the intended figure of 60 calculated to enable a 80% power to find a 15% difference in the primary outcome measure (morning PEF).

The results from the 44 patients included suggest that there may be no clinically significant difference in early morning PEF between a 5- and 10-day course of 40 mg prednisolone for adults who are taking moderate-to-high doses of a topically active inhaled steroid. Although the study fell short of its intended recruitment target,

confidence intervals for the group differences in PEF at each time of day are within  $\pm 15\%$  (60 l/min) of the mean scores. The confidence interval for worst PEF is consistent with the possibility of clinically worse outcome in the 5-day group. A larger multicentre trial is required to answer this clinically important question. The two groups of patients had similar early morning PEF at entry into the trial and throughout days 6–21. The early morning PEF of the 5-day treatment group continued to rise after day 5 when oral corticosteroids were discontinued, presumably due to the effect of their inhaled steroid therapy (9). There were no readmissions during the trial, although one patient from each group required a further course of oral corticosteroids during the study period (days 1–21). This suggests that for the two chief end points of the trial (PEF and further asthma exacerbations), there were no important differences between the two groups with this relatively small number of patients.

The two groups had similar mean symptom scores during the 5-day run-in treatment period during which all patients received 40 mg prednisolone daily. However, there was an unexplained but statistically insignificant difference between the two groups on day 5 (0.6 units on modified 7-point Likert scale). The difference

between the groups was maintained between days 6 and 21 and reached statistical significance when compared with the run-in period. The randomisation procedure resulted in a disproportionate number (5 vs. 2) of patients receiving long-acting inhaled beta-agonist treatment in the 10-day group in comparison with the 5-day group; however, a sub-analysis showed that this did not account for the difference in symptom scores between the two groups. The groups were well matched for all other demographic features, including age, sex, atopic status, duration of asthma, smoking history, theophylline use and mean predicted PEF. It is possible that the improved symptom scores in the 10-day group may represent a genuine difference between the groups due to the additional steroid treatment in this group, or a type I error in a secondary outcome measurement due to the small numbers of subjects in the study. If a small difference in symptoms does truly exist, it could be debated whether it justifies an additional 200 mg of systemic steroid treatment.

A study comparing duration of steroid treatment for adults with acute asthma found no difference in severity of symptoms, spirometric measurements or rates of readmission to hospital in patients receiving tapering courses of corticosteroids over 1 or 7 weeks (10). The use of short tapering courses has also been found to be unnecessary in acute asthma (4). The dose of 40 mg of prednisolone was chosen as it is commonly used by adult physicians (5) and is thought to be an adequate dose for the average asthmatic patient (1). The shorter course will reduce the patient's total exposure from 400 to 200 mgs of oral prednisolone, thus decreasing the risk of steroid side-effects from cumulative courses during a lifetime exposure. Even brief courses of systemic corticosteroids cause reductions in trabecular bone mineral density (11) and the cumulative effects of long-term oral steroid therapy have been shown to confer a substantial risk of vertebral fracture in patients with chronic obstructive pulmonary disease (6,7). However, a reduction in the duration of the course must maintain patient safety from acute asthma, as patients admitted to hospital with acute asthma are at increased risk of death from asthma (12).

The management of these patients requires more than just a short course of oral corticosteroids. They require intensive asthma education and a personal asthma management plan (5). All should be taking an inhaled steroid. In addition, they should be provided with a reserve course of oral corticosteroids at home with written instructions on when such treatment should be taken.

It is possible that a minority of asthma patients might benefit from a more prolonged course of oral corticosteroid therapy. However, it might be best to identify such patients individually, using agreed self-management plans based on improved PEF and symptom

scores, rather than giving prolonged courses of oral corticosteroids to every patient with acute asthma. This strategy would minimise the lifetime dose of systemic steroids for patients with asthma whilst also minimising the risk of undertreatment for individual high-risk patients.

In conclusion, the optimal duration of systemic steroid therapy for the treatment of patients with acute asthma is an important clinical question. The current study addresses this question, but has a number of short falls, in particular the small number of patients. The findings support the view that a 5-day course of 40 mg prednisolone may be sufficient for the majority of patients with acute adult asthma provided the patient is protected by medium-to-high doses of an inhaled topically active steroid and supported by a self-management plan. A large multi-centre trial based on the results of this study is clearly required to confidently answer this question.

## REFERENCES

1. Webb JR. Dose response of patients to oral corticosteroid treatment during exacerbations of asthma. *BMJ* 1986; **292**: 1045–1047.
2. Marquette CH, Stach B, Cardot E, Bervar JF, Saulnier F, Lafitte JJ, Goldstein P, Wallaert B, Tonnel AB. High-dose and low-dose systemic corticosteroids are equally efficient in acute severe asthma. *Eur Respir J* 1995; **8**: 22–27.
3. Langton Hewer S, Hobbs J, Reid F, Lenney W. Prednisolone in acute childhood asthma: clinical responses to three dosages. *Respir Med* 1998; **92**: 541–546.
4. O'Driscoll BR, Kalra S, Wilson M, Pickering CAC, Carroll KB, Woodcock AA. Double-blind trial of steroid tapering in acute asthma. *Lancet* 1993; **341**: 324–327.
5. British Thoracic Society. The British Thoracic Society guidelines on asthma management. *Thorax* 1997; **52**: s1.
6. Walsh LJ, Wong CA, Osborne J, Cooper S, Lewis SA, Pringle M, Hubbard R, Tattersfield AE. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax* 2001; **56**: 279–284.
7. McEvoy CE, Ensrud KE, Bender E, Genant HK, Yu W, Griffith JM, Niewoehner DE. Association between corticosteroid use and vertebral fractures in older men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; **57**: 704–709.
8. Quanjer H (ed.). Standardized lung function testing. *Bull Eur Physiopathol Respir* 1983; **19** (Suppl. 5): 7–10.
9. Salmeron S, Guerin JC, Godard P, Renon D, Henry-Amar M, Daroux P, Taytard A. High doses of inhaled corticosteroids in unstable asthma. *Am Rev Respir Dis* 1989; **140**: 167–171.
10. Lederle FA, Pluhar RE, Joseph AM, Niewoehner DE. Tapering of corticosteroid therapy following exacerbation of asthma. *Arch Intern Med* 1987; **147**: 2201–2203.
11. Laan RFJM, van Riel PLCM, van de Putte, van Erning LJTO, van't Hof MA, Lemmens JAM. Low-dose prednisolone induces rapid reversible axial bone loss inpatients with rheumatoid arthritis: a randomized, controlled study. *Ann Intern Med* 1993; **119**: 963–968.
12. Rea HR, Scragg R, Jackson R, Beaglehole R, Fenwick J, Sutherland DC. A case-control study of deaths from asthma. *Thorax* 1986; **41**: 833–839.